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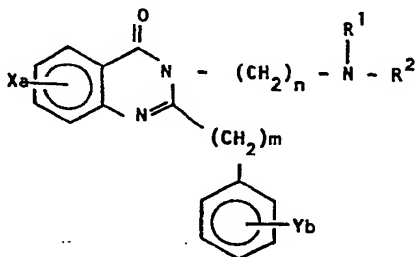
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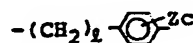
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(54) 2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinones, processes for preparing them, pharmaceutical compositions and use.

(57) Disclosed are a 2-phenylalkyl-3-aminoalkyl-4(3H)-
quinazolinone compound of Formula (1):

wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyl group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5

carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R¹ represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R² represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2)



[wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, or a halogen atom; is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R¹ and R² represent together with the nitrogen atom to which they are attached, a cyclic amin group of the formula:



/...

[wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5, or a pharmaceutically acceptable acid addition salt thereof, a process for preparing said compound, a composition comprising said compound as an active ingredient and a use of the said compound for the preparing of a pharmaceutical composition.

The compounds of the present invention have calcium antagonistic, vasodilative, and antihypertensive activities.

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2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinones,
Processes for Preparing Them, Pharmaceutical
Compositions and Use

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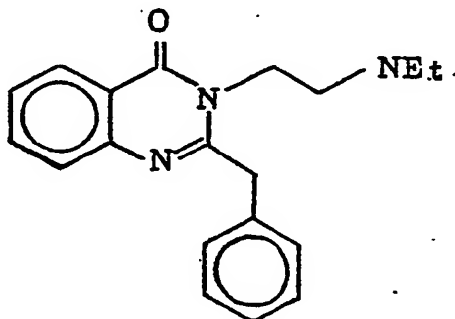
BACKGROUND OF THE INVENTION

10 This invention relates to a novel 4(3H)-quinazolinone
compound, and more particularly, a 2-phenylalkyl-
3-aminoalkyl-4(3H)-quinazolinone compound having calcium
antagonistic, vasodilative, and antihypertensive
activities, or a pharmaceutically acceptable acid addition
15 salt thereof, to a process for preparing said compound,
to a composition having calcium antagonistic activity and
comprising said compound as an active ingredient, and to
the use for preparing a composition for the dilating of
blood vessels or reducing the level of blood pressure
20 based on calcium antagonistic activity.

20

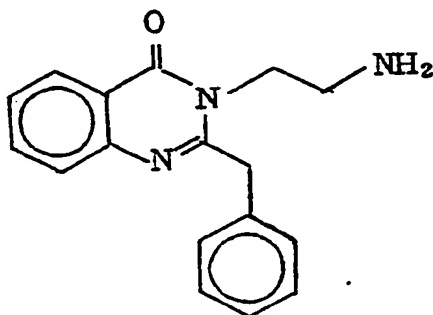
With respect to a 2-phenylalkyl-3-aminoalkyl-
4(3H)-quinazolinone derivative, there has been reported
that 2-phenylmethyl-3-(2-diethylaminoethyl)-4(3H)-
25 quinazolinone of the formula:

25



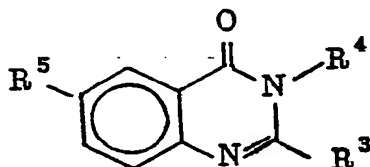
has an antispasmodic activity [Arzneim. Forsch. 13, 688 (1963)].

Moreover, although there has been known 2-phenylmethyl-3-(2-aminoethyl)-4(3H)-quinazolinone of the formula:



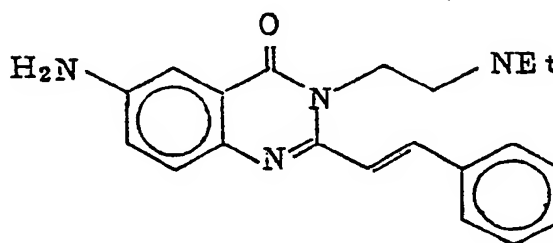
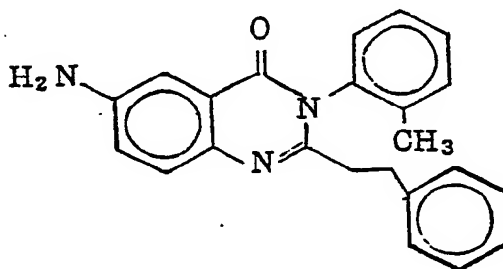
- 5 any pharmacological activity thereof has not been reported [J. Indian Chem. Soc., 57, 835 (1980)].

Further, in U. S. Patent No. 3,558,610, there has been described that a 4(3H)-quinazolinone derivative of the general formula:



- 10 wherein, R³ represents a phenyl alkyl group, etc.; R⁴ represents a di-lower alkylamino group, etc.; R⁵ represents an amino group, an alkanoylamino group, a benzylideneamino group or a nitrofurylideneamino group,

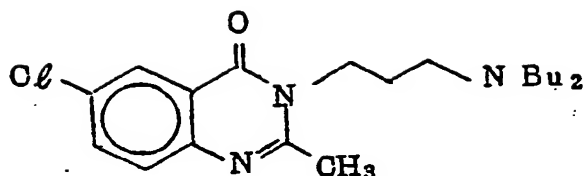
is useful as an anti-inflammatory or antimicrobial agent. However, of the compounds described in the Examples of the above Patent, compounds in which R³ is a phenylalkyl group, or R⁴ is a di-lower alkylamino group are only two
5 compounds of the following formulas:



*provided
out*

and there have been described no compounds in which R₃ is a phenylalkyl group and simultaneously R⁴ is a di-lower alkylamino group. The compounds disclosed therein are ones in which R⁵ is always an amino group or a
10 substituted amino group and are different from the compounds of the present invention.

Still further, there has been reported that 2-methyl-3-(3-dibutylaminopropyl)-6-chloro-4(3H)-quinazolinone of the following formula:

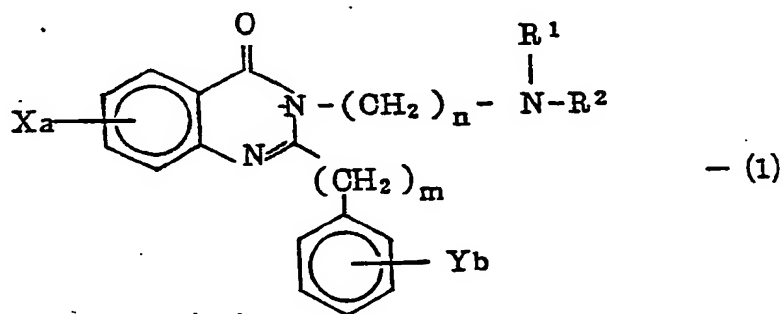


has the inhibitive activity of acetylcholinesterase, although it is not a 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative [Indian J. Pharm., 33, 80 (1971)].

5 THE SUMMARY OF THE INVENTION

An object of the present invention is to provide a novel and useful 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative.

10 Based on the knowledge described above, the present inventors have made intensive studies, and as a result, have accomplished the present invention. Namely, the novel and useful 2-phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone derivative of the present invention is a compound of Formula (1):



wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R¹ represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R² represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2)

$$-(CH_2)_\ell - \text{C}_6\text{H}_4 - Z^c$$
 [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R¹ and R² represent together with the nitrogen atom to which they are attached, a cyclic amino group of the formula:

$$-N \begin{array}{c} \text{---} \end{array} A$$
 [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

or a pharmaceutically acceptable acid addition salt thereof.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In above Formula (1), the alkyl group having 1 to 5 carbon atoms represented by X or Y includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, and a pentyl group; the alkoxy group having 1 to 5 carbon atoms represented by X or Y includes, for example, a

methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group and an isopentoxy group; and the halogen atom represented by X or Y includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

The alkyl group having 1 to 5 carbon atoms of R^1 or R^2 includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group and a pentyl group. In cases where R_2 is an aralkyl group represented by Formula (2), the alkyl group having 1 to 5 carbon atoms represented by Z includes, for example, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group and a pentyl group; the alkoxy group having 1 to 5 carbon atoms represented by Z includes, for example, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group and an n-pentoxy group; and the halogen atom represented by Z includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. The cyclic amino group of the formula: $-N \bigcirc A$, which is formed by R^1 and R^2 together with the nitrogen atom to which they are attached, includes, for example, an azolidino group, a pyrrolidino group, a piperidino group, a hexamethyleneimino group and a morpholino group. X, Y and Z each may be mono-substituted, di-substituted or tri-substituted. In cases where X is di-substituted or tri-substituted, the substituents thereof may be the same or different. In cases where Y is di-substituted or tri-substituted, the substituents thereof may be the same or different. In cases where Z is di-substituted or tri-substituted, the substituents thereof may be the same or different.

The term "pharmaceutically acceptable acid addition salt" used herein means an addition salt of an acid which does

not increase substantially toxicity of the basic compound.

5 These acid addition salts include, for example, a salt with an mineral acid such as hydrochloric acid, sulfuric acid and phosphoric acid, and with an organic acid such as acetic acid, malonic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, methanesulfonic acid, paratoluenesulfonic acid and glucuronic acid. Such an acid addition salt can be obtained by dissolving the
10 compound of the present invention in a suitable solvent and then adding thereto an acid as such or after dissolved in a suitable solvent. The suitable solvent includes, for example, ether and ethanol.

15 The compounds of the present invention have a pharmacological activity such as calcium antagonistic activity, vasodilative activity, antihypertensive activity and the like, and are useful as medical preparations for a cardiopathy and a circulatory disease.

20 Moreover, these compounds are also useful as active ingredients for pharmaceutical preparations having activities of dilating blood vessels and enhancing effects of carcinostatics based on the calcium antagonistic activity.

25 The compound of the present invention may be administered orally or parenterally to a human being in an ordinary manner. When orally administered, it is preferable to administer the compound in an amount of 1 to 100 mg per one dosage, 1 to 3 times a day; when administered by intravenous injection, it is preferable to administer the
30 compound in an amount of 0.01 to 10 mg 1 per one dosage, 1 to 5 times a day; and when administered through intestinum rectum, it is preferable to administer the compound in an amount of 1 to 100 mg per one dosage, 1 to

3 times a day. Compound (1) of the present invention or a salt thereof is generally administered in a form of a composition containing a carrier, a vehicle and the other additives usually employed for medical preparations.

5 The medical carrier may be either solid or liquid and the solid carrier includes, for example, lactose, kaoline, starch, crystalline cellulose, corn starch, talc, agar, pectin, acacia, stearic acid, magnesium stearate, lecthin, sodium chloride and the like. The liquid
10 carrier includes, for example, syrup, glycerin, peanut oil, polyvinylpyrrolidone, olive oil, ethanol, benzyl alcohol, propylene glycol, water and the like.

The medical preparations containing the compound of the present invention may take various forms. When the solid
15 carrier is used, they may take a form of tablets; powders; granules; powders or granules encapsulated in a hard gelatin; suppositories or troches.

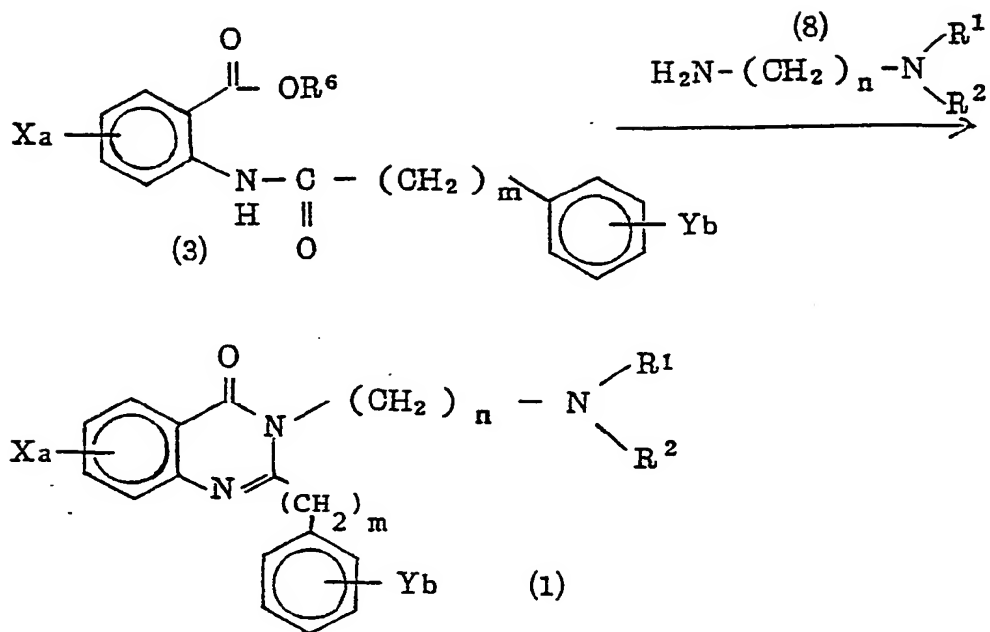
When the liquid carrier is used, the medical preparations may take a form of syrups; emulsions; soft gelatin
20 capsules; sterilized injections, for example, sealed in an ampul, or aqueous or non-aqueous suspensions.

The compound of Formula (1) of the present invention may be also used as a cyclodextrin clathrate compound or through procedures of incorporating the compound of the
25 present invention or the salt thereof in a ribosome.

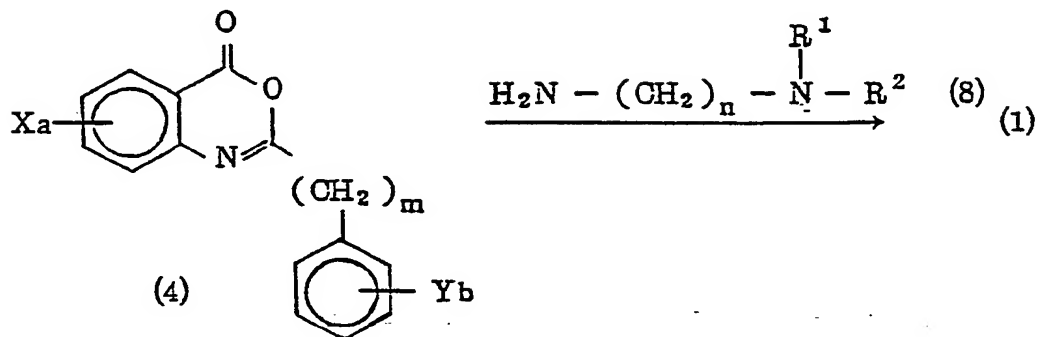
Methods for preparing the compound of the present invention will be described below.

The compound of Formula (1) of the present invention can be prepared, for example, according to the following
30 Synthesis process s A to E.

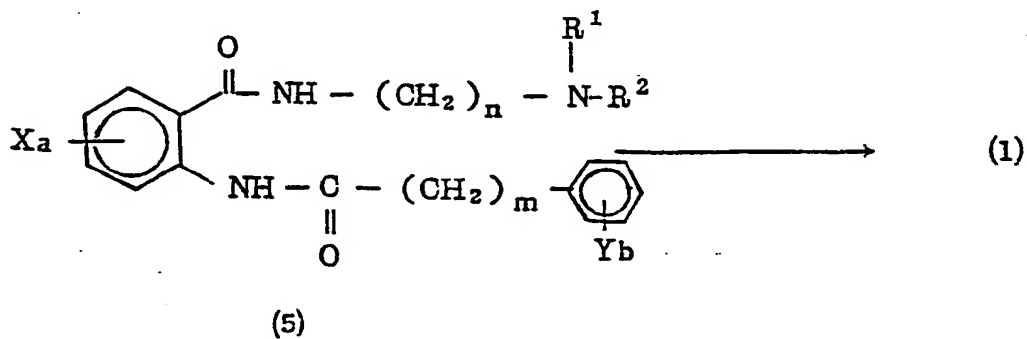
Synthesis process A



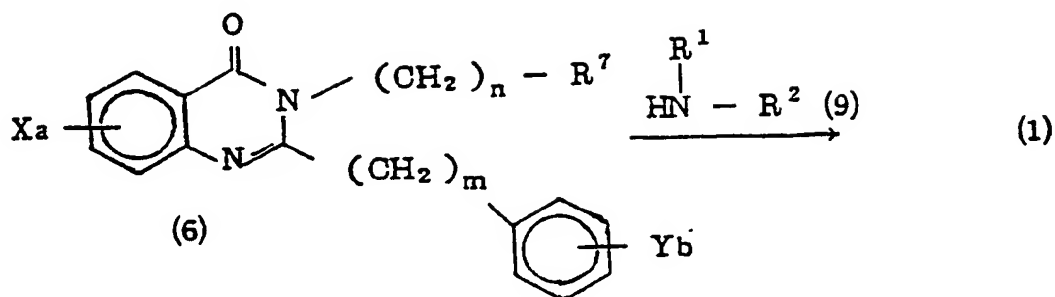
Synthesis process B



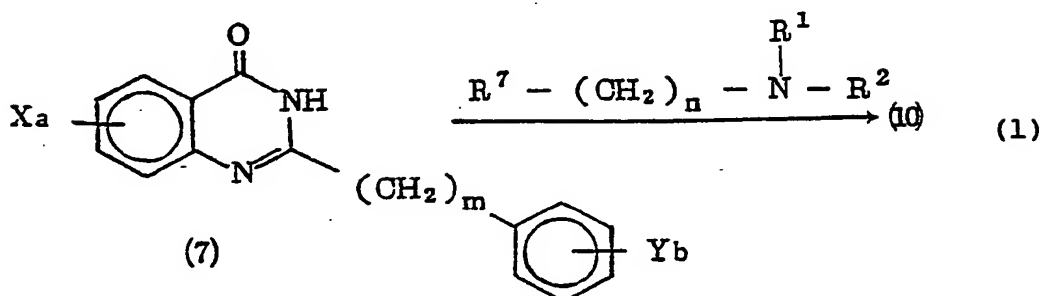
Synthesis process C



Synthesis process D



Synthesis process E



wherein, X, Y, R¹, R², a, b, m and n have the same meanings as defined above; R⁶ represents a hydrogen atom and an alkyl group having 1 to 5 carbon atoms; and R⁷ represents a halogen atom or a mesyloxy or tosyloxy group.

Synthesis process A

Synthesis process A is a method for preparing the compound of Formula (1) in which an N-(phenylalkylcarbonyl) anthranilic acid or an ester thereof (3) and a diamine (8) are condensed to form a ring therebetween. The diamine (8) may be used in an amount of 0.5 to 5 equivalent to the anthranilic acid or the ester thereof (3). The reaction solvent, although not restricted if it does not participate in the reaction, includes, for example, aromatic hydrocarbons

such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; 5 dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250°C and preferably from 100 to 200°C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If desired, an acid or a base 10 may be added to the reaction system as a catalyst.

Synthesis process B

Synthesis process B is a method for preparing the compound of Formula (1) in which a 2-phenylalkyl-4H-3,1-benzoxazine-4-one (4) and a diamine (8) are condensed 15 to form a ring therebetween. The diamine (8) may be used in an amount of 0.5 to 5 equivalent to the 4H-3,1-benzoxazin-4-one (4). The reaction solvent, although not restricted if it does not participate in the reaction, includes, for example, aromatic hydrocarbons 20 such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction 25 temperature may be in the range of from 0 to 250 °C and preferably from 50 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If desired, an acid or a base may be added to the reaction system as a catalyst.

30 Synthesis process C

Synthesis process C is a method for preparing the compound of Formula (1) in which an N-substituted

aminoalkyl-2-phenylalkylcarbonylaminobenzoic amide (5) is condensed to form a ring. The reaction may be carried out without any solvent or in an solvent which does not participate in the reaction, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; acetic anhydride; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 100 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. If the case demands, an acid may be added to the reaction system as a catalyst.

Synthesis process D

Synthesis process D is a method for preparing the compound of Formula (1) in which a 2-phenylalkyl-3-(halogenoalkyl or sulfonyloxyalkyl)-4(3H)-quinazolinone derivative (6) and an amine (9) are subjected to reaction with each other. The amine (9) may be used in an amount of 0.5 to 5 equivalent to the 4(3H)-quinanzolinone derivative (6). The reaction solvent, although not restricted if it is inert to the reaction, includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol and isoamyl alcohol; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethylformamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 50 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. When the reaction is carried out, an excess of the amine (9),

for example, an organic amine such as triethylamine, pyridine, diazacycloundecene (DBU), or an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogencarbonate should preferably be present in the reaction system as an acid removing agent, for the smooth progress of the reaction.

Synthesis process E

Synthesis process E is a method for preparing the compound of Formula (1) in which a 2-phenylmethyl-4(3H)-quinazolinone (7) and an aminoalkyl halide (or an aminoalkyl sulfonate) (10) are subjected to reaction with each other. The aminoalkyl halide (or the aminoalkyl sulfonate) (10) may be used in an amount of 0.5 to 5 equivalent to the 4(3H)-quinazolinone (7). The reaction solvent, although not restricted if it is inert to the reaction, includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; alcohols such as methanol, ethanol and isoamyl alcohol; ethers such as tetrahydrofuran, dioxane and ethylene glycol diethyl ether; ketones such as acetone and methyl ethyl ketone; ethyl acetate; dimethyl-formamide; dimethylacetamide; dimethyl sulfoxide and the like. The reaction temperature may be in the range of from 0 to 250 °C and preferably from 50 to 150 °C. The reaction time may be in the range of from 30 minutes to 48 hours and preferably 1 to 24 hours. When the reaction is carried out in the presence of a base such as sodium metal, sodium hydride, potassium t-butoxide, the reaction proceeds smoothly.

Next, the present invention will be explained more specifically by the following Examples, by which however the present invention should not be limited.

Example

Synthesis example 1

N-(2-Methoxyphenylacetyl)-anthranilic acid methyl ester:

To a mixed solution of acetone (300 ml) and a 6 % aqueous
5 potassium carbonate solution (200 ml) there were added
10.2 g (67 mmol) of methyl ester of anthranilic acid.
12.5 g (67 mmol) of 2-Methoxyphenylacetic acid chloride
were added dropwise under cooling thereto and the
resulting reaction mixture was stirred at room
10 temperature for 4 hours. The resulting precipitates were
collected by filtration to obtain 15.7 g (yield 78 %) of
N-(2-methoxyphenylacetyl)-anthranilic acid methyl ester.

m.p. : 116 - 117 °C.

Example 1

15 2-(2-Methoxyphenylmethyl)-3-(2-diethylaminoethyl)-4(3H)-
quinazolinone hydrochloride (Compound No.1; Synthesis
process A)

A solution of 3.0 g (10 mmol) of methyl ester of
N-(2-methoxyphenyl-acetyl)-anthranilic acid and 5.1 g (50
20 mmol) of 2-diethylaminoethylamine in ethanol (20 ml) was
heated at 180°C for 7 hours in a sealed tube. After
cooling, the thus obtained reaction mixture was purified
by silica gel column chromatography (eluent; chloroform :
ethanol = 98 : 2) to obtain 1.24 g (yield 34 %) of
25 2-(2-methoxyphenylmethyl)-3-(2-diethylaminoethyl)-4(3H)-
quinazolinone as an oily substance. 1.2 g of the oily
substance were dissolved in ethanol (5 ml) and a 7 %
HCl-ethanol solution (1.5 ml) were added thereto. The
resulting solution was allowed to cool overnight. The

m.p.: 196 - 209 °C (decomposition)

Analysis Calculated for $C_{22}H_{27}N_3O_2 \cdot HCl$:

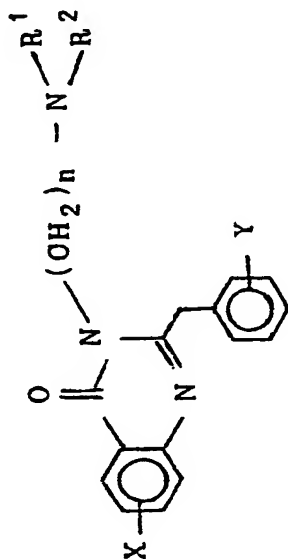
10 Found: C, 65.57; H, 7.01; N, 10.44 %

2-(Substituted phenylmethyl)-3-(substituted aminoalkyl)-4
(3H)-quinazolinone derivatives (Compound Nos. 2 to 29)

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Table 1

Example No.	Compound No.	X	Y	$\begin{matrix} R^1 \\ N \\ R^2 \end{matrix}$	n	Discrimination between free base and salt	Ester form of starting material	Yield (%)	Melting point (°C)	Infrared absorption spectrum (cm ⁻¹)
2	2	hydrogen atom	2-chloro	diethylamino	2	hydrochloride	ethyl	57	188-193	1665 1590
3	3	"	4-chloro	"	2	"	methyl	10	175-178	1670 1585
4	4	"	2-chloro	"	2	"	ethyl	36	191-194	1670 1590
5	5	"	3-chloro	"	2	"	methyl	36	210-213	1675 1590
6	6	"	4-chloro	"	2	fumarate	ethyl	14	160-165	1675 1590
7	7	"	4-bromo	"	2	free base	methyl	27	(oily)	1670 1590
8	8	"	4-methoxy	"	2	"	ethyl	61	(oily)	1670 1590
9	9	"	2-ethoxy	"	2	hydrochloride	methyl	17	159-162	1665 1585
10	10	"	4-ethoxy	"	2	"	"	42	173-184	1670 1585
11	11	"	4-methyl	"	2	"	ethyl	62	162-168	1660 1590
12	12	"	4-nitro	"	2	free base	"	9	114-122	1665 1585
13	13	"	2,5-dimethoxy	"	2	hydrochloride	"	42	179-181	1670 1590



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Table 1 (Contd.)

Example No.	Compound No.	X	Y	$\begin{matrix} R^1 \\ \diagup \\ N \\ \diagdown \\ R^2 \end{matrix}$	n	Discrimination between free base and salt	Ester form of starting material	η_{inh}^{25} (%)	Melting point (°C)	Infrared absorption spectrum (cm ⁻¹)
14	14	hydrogen atom	2,5-dimethoxy	diethyl-amino	3	hydrochloride	methyl	8	120-124	1675 1590
15	15	"	"	pyrrolidino	2	"	"	25	124-128	1670 1585
16	16	"	"	dimethyl-amino	2	"	"	23	189-194	1660 1580
17	17	"	"	"	3	"	"	14	212-216	1665 1595
18	18	"	3,4-dimethoxy	diethylamino	2	free base	ethyl	77	(oily)	1660 1585
19	19	"	2-benzyloxy	"	2	hydrochloride	methyl	30	182-189	1665 1585
20	20	"	4-benzyloxy	"	2	"	"	45	137-138	1670 1590
21	21	6-methyl	2,5-dimethoxy	"	2	"	"	13	152-155	1660 1580
22	22	"	"	"	3	free base	"	20	(oily)	1660 1580
23	23	"	"	morpholino	3	"	"	24	(")	1665 1585
24	24	"	"	dimethyl-amino	2	hydrochloride	"	13	187-198	1655 1575
25	25	6-iodo	2-methoxy	diethylamino	2	"	"	54	189-194	1670 1585
26	26	"	2,5-dimethoxy	"	2	"	"	49	164-168	1670 1585
27	27	"	4-ethoxy	"	2	"	"	60	193-195	1670 1580
28	28	6-chloro	2,5-dimethoxy	"	2	"	"	44	162-163	1670 1585
29	29	7-chloro	"	"	2	"	"	46	146-150	1680 1590

Synthesis example 2

2-(2,5-Dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1,-
benzoxazin-4-one

To a suspension of 9.8 g (50 mmol) of 5-isopropoxy-2-aminobenzoic acid and 11.0 g (80 mmol) of potassium carbonate in a mixed solvent of acetone (40 ml) and water (40 ml), 10.5 g (50 mmol) of 2,5-dimethoxyphenylacetic acid chloride were added dropwise at 10 °C. After the resulting reaction mixture was stirred under ice cooling for 1 hour, stirring was continued for further 2 hours at room temperature. The thus obtained solution was made acidic with conc. hydrochloric acid and extracted with dichloromethane. After the extract was dried over magnesium sulfate, the solvent was distilled off to obtain 14.0 g (75%) of 2-(2,5-dimethoxyphenyl-acetylamino)-5-isopropoxybenzoic acid (m.p. 132 - 135 °C). Then the thus obtained acid was heated under reflux for 2 hours in acetic anhydride (100 ml), followed by concentration under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane) to obtain 6.8 g of 2-(2,5-dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1-benzoxazine-4-one (yield from 5-isopropoxy-2-aminobenzoic acid: 36 %)

m.p. 84 - 87 °C

Infrared absorption spectrum (cm⁻¹): 1745, 1630

Example 30

2-(2,5-Dimethoxyphenylmethyl)-3-(3-dimethylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone maleate (Compound No. 30; Synthesis process B)

- 5 2.84 g (8 mmol) of 2-(2,5-dimethoxyphenylmethyl)-6-isopropoxy-4H-3,1-benzoxazin-4-one and 0.82 g (8 mmol) of 3-dimethylaminopropylamine were heated under reflux for 15 hours in xylene (20 ml). After the xylene was distilled off, the residue obtained was purified by
10 silica gel column chromatography (eluent; 2 % ethanol/chloroform) to obtain 1.46 g (42 %) of 2-(2,5-dimethoxyphenylmethyl)-3-(3-dimethylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone as an oily substance. Subsequently, 0.22 g of the 2-(2,5-dimethoxyphenylmethyl)-3-(3-dimethylamino-
15 -propyl)-6-isopropoxy-4(3H)-quinazolinone was dissolved in ether (15 ml) and to the resulting solution, there was added an ethanolic solution containing 0.07 g (0.6 mmol) of maleic acid. The thus obtained solution was allowed to stand for one day. The precipitated colorless crystals
20 were collected by filtration to obtain 0.25 g of the maleate which is the desired compound.

m.p.: 188 - 189 °C

Mass spectrum (m/e): 439 (M⁺),
58 (Base peak ion)

25 Analysis Calculated for C₂₅H₃₃N₃O₄·C₄H₄O₄:

C, 62.68; H, 6.71; N, 7.56 %

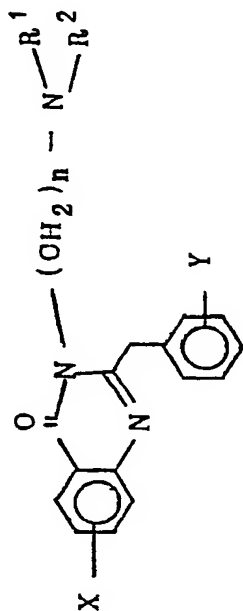
Found: C, 62.48; H, 6.71; N, 7.57 %

Examples 31 to 88

2-(Substituted phenylmethyl)-3-(substituted aminoalkyl)-4-(3H)-quinazolinone derivatives, (Compound Nos.31 to 88)

5 The captioned compounds were synthesized in the same manner as in Example 30 except that the 2-(2,5-dimethoxy-phenylmethyl)-6-isopropoxy-4H-3,1-benzoxazin-4-one was replaced by the corresponding 4H-3,1-benzoxazin-4-one, and the 3-dimethylaminopropylamine was replaced by the
10 in Table 2.

Table 2



Example No.	Compound No.	X	Y	R ¹ N R ²	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e)	
									M ⁺	Base peak ion
31	31	6-methyl	2,5-dimethoxy	pyrrolidino	2	fumarate	75	169-170	407	84
32	32	"	"	"	3	free base	54	oily	421	84
33	33	6-ethyl	"	dimethylamino	3	"	50	"	409	58
34	34	"	"	diethylamino	3	"	48	"	437	86
35	35	7-chloro	"	dimethylamino	3	hydrochloride	90	186-192	415	58
36	36	"	"	pyrrolidino	3	free base	45	oily	441	84
37	37	"	"	diethylamino	3	"	68	"	443	86
38	38	6-hydroxy	"	pyrrolidino	2	"	38	"	409	84
39	39	"	"	dimethylamino	3	"	38	"	397	58
40	40	6-methoxy	"	"	3	"	5	"	411	58
41	41	6-ethoxy	2-methoxy	"	2	hydrochloride	83	209-216	381	58

Table 2 (Contd.)

Example No.	Compound No.	X	Y	$\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^2 \end{array}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e)	
									M ⁺	Base peak ion
42	42	6-ethoxy	4-methoxy	dimethylamino	2	hydrochloride	83	235-240	381	58
43	43	"	2,5-dimethoxy	"	2	"	83	214-217	411	58
44	44	6-n-propoxy	"	pyrrolidino	2	"	69	132-137	416	84
45	45	"	"	diethylamino	2	"	82	154-159	453	86
46	46	6-isopropoxy	"	pyrrolidino	2	"	32	141-147	451	84
47	47	"	"	dimethylamino	2	"	61	184-188	425	58
48	48	"	"	diethylamino	2	"	76	154-158	453	86
49	49	"	"	pyrrolidino	3	"	48	125-130	465	84
50	50	"	"	dimethylamino	2	"	46	195-199	395	58
51	51	"	4-methoxy	"	2	free base	50	oily	399	58
52	52	"	2-chloro	"	2	"	51	"	389	58
53	53	"	4-chloro	"	3	"	35	"	409	58
54	54	"	4-methoxy	"	3	hydrochloride	51	184-188	453	58
55	55	6-n-butoxy	2,5-dimethoxy	"	2	"	89	166-173	465	84
56	56	"	"	pyrrolidino	2	"	53	150-157	468	86
57	57	"	"	diethylamino	2	"	83	130-138	439	58
58	58	"	"	dimethylamino	2	"	33	154-161	465	84
59	59	6-isobutoxy	"	pyrrolidino	2	"	31	oily	453	58
		"	"	dimethylamino	3	free base				

Table 2 (Contd.)

Example No.	Compound No.	X	Y	$\begin{matrix} R^1 \\ \diagup \\ N \\ \diagdown \\ R^2 \end{matrix}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e) Base peak ion
60	60	6-sec-butoxy	2,5-dimethoxy	dimethyl-amino	3	free base	31	oily	453 58
61	61	"	"	pyrrolidino	2	hydrochloride	57	147-153	465 84
62	62	"	"	diethylamino	2	free base	19	oily	467 86
63	63	"	"	dimethylamino	2	hydrochloride	92	116-125	439 58
64	64	"	"	"	3	"	71	185-190	453 58
65	65	6-n-pentoxy	"	"	3	"	72	210-214	467 58
66	66	"	"	pyrrolidino	2	"	68	127-135	479 84
67	67	"	"	"	3	free base	60	oily	493 84
68	68	"	"	dimethylamino	3	"	63	"	495 86
69	69	"	"	"	2	hydrochloride	59	123-129	481 86
70	70	"	"	"	2	"	70	141-150	453 58
71	71	6-isopentoxy	"	pyrrolidino	2	"	82	140-148	479 84
72	72	"	"	"	3	"	59	99-103	493 84
73	73	"	"	dimethylamino	3	free base	56	oily	467 58
74	74	"	"	"	2	hydrochloride	65	129-137	453 58
75	75	"	"	diethylamino	2	"	63	131-138	481 86
76	76	"	"	"	3	free base	43	oily	495 86

Table 2 (Contd.)

Example No.	Compound No.	X	Y	N $\begin{smallmatrix} \nearrow R^1 \\ \searrow R^2 \end{smallmatrix}$	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e)	
									M ⁺	Base peak ion
77	77	6,7-dimethoxy	2,5-dimethoxy	dimethylamino	2	free base	64	oily	427	58
78	78	"	4-methoxy	"	2	"	73	"	397	58
79	79	6-methoxy-7-isopropoxy	2,5-dimethoxy	"	2	"	62	"	455	58
80	80	"	4-methoxy	"	2	"	45	"	425	58
81	81	6-isopropoxy-7-methoxy	2,5-dimethoxy	"	2	"	77	115-118	455	58
82	82	"	4-methoxy	"	2	hydrochloride	58	235-239	425	58
83	83	"	"	methylamino	2	free base	28	oily	411	355
84	84	6-ethoxy-7-methoxy	"	dimethylamino	2	"	77	"	411	58
85	85	"	"	"	3	"	77	"	425	58
86	86	6-isopropoxy	2-methoxy	"	2	hydrochloride	70	178-183	395	58
87	87	6-isopropoxy-7-methoxy	"	"	2	"	97	200-203	425	58
88	88	6-phenoxy	2,5-dimethoxy	"	2	"	49	184-187	459	58

Synthesis example 3

2-(2-Methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one

Following the same procedure as in Synthesis example 2,
2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was
5 obtained from anthranilic acid and 2-(methoxyphenylacetic
acid chloride as starting materials via 2-(2-
methoxyphenylmethylcarbonyl amino)benzoic acid as an
intermediate (yield: 60 %).

m.p. 102 - 104 °C
10 Mass spectrum (m/e): 267 (M⁺),
146 (Base peak ion)
Infrared absorption spectrum (cm⁻¹): 1740, 1635,
1595

Example 89

15 2-(2-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenyl-
ethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone
hydrochloride (Compound No. 89; Synthesis process B)

268 mg (1 mmol) of 2-(2-methoxyphenylmethyl)-4H-3,1-
benzoxazine-4-one and 238 mg (1 mmol) of 2-[[N-[2-(3,4-
20 dimethoxyphenyl)ethyl]-N-methylamino]]ethyl-amine were
heated in xylene (10 ml) under reflux for 10 hours .
After the xylene was distilled off, the residue obtained
was purified by silica gel column chromatography (eluent;
2 % ethanol/chloroform) to obtain 107 mg (52 %) of
25 2-(2-methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenyl-
ethyl)-N-methylamino}ethyl]-4(3H)-quinazolinone as an
oily substance. Subsequently, the thus obtained
quinazolinone was dissolved in ethanol (2 ml) and to the
resulting solution there was added a 7 % hydrogen
30 chloride-ethanol solution (1 ml). Further, ether was

added to the reaction mixture thus obtained, and the precipitated colorless crystals were collected by filtration to obtain 99 mg of the hydrochloride which is the desired compound.

5 m.p.: 171 - 175 °C (decomposition)

Mass spectrum (m/e): 487 (M⁺),
293 (Base peak ion)

Analysis Calculated for C₂₉H₃₃N₃O₄·HCl:

C, 66.46; H, 6.54; N, 8.02 %

10 Found: C, 66.23; H, 6.75; N, 7.89 %

Examples 90 to 132

2-(Substituted phenylmethyl)-3-[N-alkyl-N-(substituted phenylalkyl)aminoalkyl]-4(3H)-quinazolinone derivatives
(Compound Nos. 90 to 132)

- 15 The captioned compounds were synthesized in the same manner as in Example 89 except that the 2-(2-methoxyphenylmethyl)-4H-3,1-benzoxazin-4-one was replaced by the corresponding 4H-3,1-benzoxazin-4-one derivatives, and the 2-[N-(2-(3,4-dimethoxyphenyl)ethyl)-
- 20 N-methylamino]ethylamine was replaced by the corresponding N-alkyl-N-(substituted phenylalkyl)aminoalkylamines. The results obtained are shown in Table 3.

Table 3

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</div><div>N</div><div>-</div><div>(OH₂)_n</div><div>-</div><div>N</div><div>-</div><div>(CH₂)₂</div><div>-</div><div>Z</div></div><div><div><div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></di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Table 3 (Contd.)

No.	X	Y	R ¹	Z	n	l	Discrimina- tion between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e)	
										Base peak M ⁺ ion	
102	6-isopropoxy	2,5-dimethoxy	methyl	3,4-dimethoxy	2	2	free base	14	oily	575	381
103	"	"	"	"	3	2	"	11	"	589	395
104	"	"	"	hydrogen atom	3	2	"	9	"	529	395
105	6-sec-butoxy	"	"	3,4-dimethoxy	2	2	"	29	"	-	265
106	6-(4-chlorophenoxy)	"	"	"	2	2	hydrochloride	36	106-111	643	449
107	6-(4-methoxyphenoxy)	"	"	"	2	2	"	23	100-106	639	445
108	hydrogen atom	"	"	"	3	2	free base	37	oily	531	265
109	6-n-butoxy	"	"	"	2	2	"	33	"	589	395
110	6-n-pentoxy	"	"	"	2	2	"	29	"	603	409
111	6-isopentoxy	"	"	"	2	2	"	26	"	603	409
112	hydrogen atom	4-methoxy	"	"	2	2	"	31	"	487	293
113	"	2-chloro	"	"	2	2	"	17	"	-	297
114	6-methyl	2,5-dimethoxy	"	"	2	2	"	21	"	531	337
115	hydrogen atom	3,4-dimethoxy	"	"	2	2	"	43	"	517	323
116	6-iodo	2,5-dimethoxy	"	"	2	2	"	56	"	643	449
117	6-isopropoxy	2-methoxy	"	"	2	2	"	37	"	545	381
118	"	4-methoxy	"	"	2	2	"	37	"	545	381
119	"	2-chloro	"	"	2	2	"	40	"	549	381

Table 3 (Contd.)

No.	X	Y	R ¹	Z	n	Discrimina- tion between free base and salt	Phen (%)	Melting point (°C)	Mass spectrum (m/e) Base + peak M ⁺ ion
120	6-isopropoxy	3,4-dimethoxy	methyl	3,4-dimethoxy	2	free base	51	oily	575 381
121	6-ethoxy	2,5-dimethoxy	"	"	2	"	22	"	561 367
122	6-methoxy	"	"	"	2	"	51	"	547 353
123	hydrogen atom	"	"	3-methoxy	2	"	14	"	487 323
124	6-isopropoxy	"	"	"	2	"	13	"	545 381
125	hydrogen atom	"	"	4-methyl	2	"	22	"	471 323
126	6-isopropoxy	"	"	"	2	"	18	"	529 381
127	"	"	"	4-methoxy	2	"	28	"	545 381
128	hydrogen atom	"	"	4-chloro	2	"	20	"	491 323
129	6-isopropoxy	"	"	"	2	"	9	"	549 381
130	hydrogen atom	"	"	2,5-dimethoxy	2	"	26	"	517 323
131	6-isopropoxy	"	"	"	2	"	17	"	575 381
132	hydrogen atom	"	"	4-methoxy	2	"	48	"	487 323

Synthesis example 4

2-(2,5-Dimethoxyphenylacetyl-amino)-5-methyl-N-(2-dimethyl-aminoethyl)benzamide

0.50 g (1.5 mmol) of 2-(2,5-dimethoxyphenylacetyl-amino)-
5-methylbenzoic acid (m.p. 163 to 164.5 °C) synthesized
in the same manner as in Synthesis example 1 for
2-(2,5-dimethoxyphenylacetyl-amino)-5-isopropoxy-
benzoic acid was suspended in dichloromethane (10 ml),
and then to the resulting mixture was added dropwise a
dichloromethane solution containing 0.33 (1.6 mmol) of
dicyclohexylcarbodiimide (DCC) under ice cooling.
Subsequently, 0.14 g (16 mmol) of 2-dimethyl-
aminoethylamine was added dropwise thereto and the
mixture thus obtained was stirred for 2 hours at room
temperature. The precipitates were filtered off and the
mother liquid was concentrated by distillation. The thus
obtained residue was purified by silica gel column
chromatography (eluent; dichloromethane : ethanol=97 : 3)
to obtain 0.41 g (yield 68 %) of 2-(2,5-dimethoxyphenyl-
acetyl-amino)-5-methyl-N-(2-dimethylaminoethyl)benzamide.

m.p. 105 - 110°C

Example 133

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone hydrochloride (Compound No.24; Synthesis process C)

0.37 g (1 mmol) of 2-(2,5-dimethoxyphenylacetyl-amino)-
N-(2-dimethylaminoethyl)benzamide and 200 mg of
para-toluenesulfonic acid were heated in xylene (20 ml)
under reflux for 3 hours. The reaction mixture thus
obtained was purified by silica gel column chromatography
(eluent; 2 % ethanol/chloroform) to obtain 70 mg (20 %)

of 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone as an oily substance.

Subsequently, the thus obtained oily substance was dissolved in 1 ml of ethanol, and to the resulting solution was added a 7 % hydrogen chloride-ethanol solution (2 ml). Further, ether was added to the reaction mixture thus obtained and the precipitated colorless crystals were collected by filtration to obtain 70 mg of the hydrochloride which is the desired compound. The melting point and infrared absorption spectrum of the above hydrochloride was identical with those of Compound 24 synthesized in Example 24, respectively.

Synthesis example 5

2-(2-Methoxyphenylmethyl)-3-(2-chloroethyl)-4(3H)-quinazolinone

A suspension of 3.0 g (10 mmol) of methyl ester of N-(2-methoxyphenylacetyl)anthranilic acid and 1.2g (20 mmol) of monoethanolamine in xylene was heated at 180. °C for 16 hours in a sealed tube. After cooling, the precipitated crystals were collected by filtration to obtain 0.7g (22 %) of 2-(2-methoxyphenylmethyl)-3-(2-hydroxyethyl)-4(3H)-quinazolinone (m.p.: 154 - 155 °C). Subsequently, to 0.7 g (2.2 mmol) of this 3-(2-hydroxyethyl) derivative was added thionyl chloride (5ml) and the resulting reaction mixture was stirred at room temperature for 1 hour. An excess of the thionyl chloride was distilled off under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent: dichloromethane) to obtain 0.14 g (20%) of 2-(2-methoxyphenylmethyl)-3-(2-chloroethyl)-4(3H)-quinazolinone. (m.p.: 109 - 111 °C).

Example 134

2-(2-Methoxyphenylmethyl)-3-(2-ethylaminoethyl)-4(3H)-quinazolinone (Compound No. 133; Synthesis process D)

A mixture of 328 mg (1 mmol) of 2-(2-methoxyphenylmethyl)
5 -3-(2-chloroethyl)-4(3H)-quinazolinone and a 70 % aqueous
ethylamine solution (0.6 ml) in ethanol (10 ml) was
heated at 80 °C for 8 hours in a sealed tube. The
solvent was distilled off under reduced pressure and to
the residue thus obtained there was added a 10 % aqueous
10 potassium carbonate solution, followed by extraction with
dichloromethane. The thus obtained dichloromethane
solution was dried over magnesium sulfate and then
concentrated. The resulting residue was purified by
silica gel column chromatography (eluent: 1 %
15 ethanol-chloroform) to obtain 55 mg (16%) of
2-(2-methoxyphenylmethyl)-3-(2-ethylaminoethyl)-4(3H)-
quinazolinone as an oily substance. Subsequently, the
thus obtained quinazolinone was dissolved in ether (3 ml)
and to the resulting solution was added a 10% HCl/ethanol
20 solution. The precipitated crystals were collected by
filtration to obtain the hydrochloride of the captioned
compound.

m.p.: 170 - 175 °C

Mass spectrum (m/e): 337 (M⁺),
25 267 (Base peak ion)

Examples 135 to 136

2-(2-Methoxyphenylmethyl)-3-(substitued aminoalkyl)-
4(3H)-quinazolinone derivatives (Compound Nos. 134 and
135)

- 5 The captioned compounds were synthesized in the same manner as in Example 134 except that the 70 % aqueous ethylamine solution was replaced by the corresponding amines, respectively. The results obtained are shown in Table 4.

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Table 4

Example No.	Compound No.	X	Y	R ¹ N R ²	n	Discrimination between free base and salt	Yield (%)	Melting point (°C)	Mass spectrum (m/e)	
									M +	Base peak ion
135	134	hydrogen atom	2-methoxy	cyclopentylamino	2	free base	41	oil	377	267
136	135	"	"	hexamethyleneimino	2	hydrochloride	50	135-145	-	112

Synthesis example 6

2-(2,5-dimethoxyphenylmethyl)-6-methyl-4(3H)-quinazolinone

A mixture of 3.15 g (9.6 mmol) of 2-(2,5-dimethoxy-phenylacetyl-amino)- 5-methylbenzoic acid (m.p. 163 to
 5 164.5 °C) obtainble by the same method as in Synthesis
 example 2 and 0.90 g (20ml) of formamide were heated at
 160 °C for 3 hours. After cooling, the solidified
 residue was added to a mixed solution of ethanol (100 ml)
 and acetone (100 ml) and dissolved therein by heating.
 10 After cooling, the precipitated crystals were collected
 by filtration to obtain 1.45 g (yield 49 %) of 2-(2,5-
 dimethoxyphenylmethyl)-6-methyl-4(3H)-quinazolinone.

m.p.: 188 - 189 °C

Mass spectrum (m/e): 310 (M⁺),
 15 279 (Base peak ion)

Example 138

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-
 methyl-4(3H)-quinazolinone hydrochloride (Compound No.
 24; Synthesis process E)

20 A suspension of 0.62 g (2 mmol) of 2-(2,5-dimethoxy-
 phenylmethyl)-6-methyl-4(3H)-quinazolinone and 0.19 g (2
 mmol) of 50 % sodium hydride in dioxane (10 ml) were
 stirred at room temperature for 1 hour. Then, to the
 resulting reaction mixture was added 0.22 g (2 mmol) of
 25 dimethylaminoethyl chloride dissolved in dioxane (10 ml),
 followed by heating at 60 °C for 5 hours. After cooling,
 to the mixture obtained were added 30 ml of water. The
 resulting mixture was extract d with dichloromethane and

the dichloromethane layer was concentrated under reduced pressure. The thus obtained residue was purified by silica gel column chromatography (eluent; dichloromethane: ethanol = 97 : 3) to obtain 0.10 g (yield 13 %) of 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone as an oily substance. The thus obtained quinazolinone was dissolved in ether and to the resulting solution was added a 5 % hydrogen chloride-ethanol solution and the precipitated crystals were collected by filtration to obtain 2-(2,5-dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-methyl-4(3H)-quinazolinone hydrochloride. The melting point and infrared absorption spectrum of this hydrochloride were identical with those of Compound 24 obtained in Example 24, respectively.

Example 139

2-(2,5-Dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-benzyloxy-4(3H)-quinazolinone (Compound No. 136)

2-(2,5-dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-hydroxy-4(3H)-quinazolinone (Compound No. 38) (90 mg, 0.2 mmol) and sodium hydroxide (16 mg, 0.4 mmol) were added to a mixed solvent of ethanol (10 ml) and water (5 ml). To the resulting reaction mixture were added benzyl chloride (40 mg, 0.3 mmol), followed by reflux for 1 hour, and then, to the mixture thus obtained further were added benzyl chloride (27 mg, 0.2 mmol), followed by reflux for further 1.5 hours. After concentration under reduced pressure, water was added thereto and the mixture obtained was extracted with dichloromethane. The dichloromethane solution was dried over magnesium sulfate and purified by silica gel column chromatography (eluent; ethanol (0 - 5%)-dichloromethane) to obtain 16 mg (15%) of 2-(2,5-dimethoxyphenylmethyl)-3-{2-(1-pyrrolidino)ethyl}-6-benzyloxy-4(3H)-quinazolinone.

Mass spectrum (m/e): 499 (M^+),
84 (Base peak ion)

Infrared absorption spectrum (IR) (cm^{-1}):
1655, 1585

5 Example 140

3-(2-Dimethylaminoethyl)-2-{2-(4-methoxyphenyl)ethyl}-4
(3H)-quinazolinone (Compound No. 137; Synthesis process
B)

10 A mixture of 295 mg (1 mmol) of 2-{2-(4-methoxyphenyl)
ethyl}-4H-3,1-benzoxazin-4-one synthesized in the same
manner as in Synthesis example 2 and 88 mg (1 mmol) of
2-dimethylaminoethylamine in xylene (5 ml) was heated
under reflux for 2 hours. After the xylene was distilled
15 off under reduced pressure, the crude crystals obtained
were purified by silica gel column chromatography
(eluent; 3 % methanol/methylene chloride) to obtain 260
mg (76 %) of 3-(2-dimethylaminoethyl)-2-{2-(4-
methoxyphenyl)ethyl}-4(3H)-quinazolinone.

m.p.: 73.5 - 74.5 °C

20 Mass spectrum (m/e): 351 (M^+),
58 (Base peak ion)

Infrared absorption spectrum (IR) (cm^{-1}):
1665 (C=O), 1600 (phenyl group)

Example 141

3-(2-Dimethylaminoethyl)-6-isopropoxy-7-methoxy-2-
{3-(4-methoxyphenyl)propyl}-4(3H)-quinazolinone (Compound
No. 138, Synthesis process B)

- 5 A mixture of 384 mg (1 mmol) of 6-isopropoxy-7-methoxy-2-
{3-(4-methoxyphenyl)propyl}4H-3,1-benzoxazin-4-one
synthesized in the same manner as in Synthesis example 2
and 88 mg (1 mmol) of 2-dimethylaminoethylamine in xylene
(5 ml) was heated under reflux for 2 hours. After the
10 xylene was distilled off, the crude crystals obtained
were purified by silica gel column chromatography
(eluent; 3 % methanol/methylene chloride) to obtain 362
mg (80 %) of 3-(2-dimethylaminoethyl)-6-isopropoxy-7-
methoxy-2-{3-(4-methoxyphenyl)propyl}-4(3H)-
15 quinazolinone.

m.p.: 65.5 - 66.5 °C

Mass spectrum (m/e): 453 (M⁺),
58 (Base peak ion)

m.p.: 65.5 - 66.5 °C

- 20 Mass spectrum (m/e): 453 (M⁺),
58 (Base peak ion)

Infrared absorption spectrum (IR) (cm⁻¹):
1660 (C=O), 1605 (phenyl group)

Example 142

2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-4
(3H)-quinazolinone hydrochloride (Compound No. 16;
Synthesis process A)

- 5 A mixture of 0.62 g (2 mmol) of N-(2,5-dimethoxyphenyl-
acetyl) anthranilic acid and 0.36 g (3 mmol) of
2-dimethylaminoethylamine in xylene (5 ml) were heated
under reflux for 24 hours. After cooling, the resulting
reaction mixture was purified by silica gel column
10 chromatography (eluent; chloroform: ethanol = 98 : 2) to
obtain 0.10 g (yield 14 %) of 2-(2,5-dimethoxy-
phenylmethyl)-3-(2-dimethylaminoethyl)-4(3H)
quinazolinone as an oily substance. 0.10 g of the oily
substance thus obtained was dissolved in ethanol (1 ml)
15 and then a 7 % HCl-ethanol solution (0.2 mol) was added
thereto and the resulting reaction mixture was cooled
overnight. The resulting colorless precipitates were
collected by filtration to obtain 0.1 g of the
hydrochloride which is the desired compound. This
20 hydrochloride coincides with the compound obtained in
Example 16 in melting point and infrared absorption
spectrum.

Application example 1

Calcium antagonistic activity

- 25 Calcium antagonistic activity of the present compound was
investigated by observing the effects on the calcium
induced contraction of the isolated thoracic aorta in
rats.

- A piece of thoracic aorta was isolated from male Wistar
30 strain rats weighing 350 - 450 g in order to prepare a

5 spiral specimen. This specimen was suspended in a Krebs-Henseleit solution free from calcium. The contraction was evoked by an application of CaCl_2 in the presence of 80 mM potassium so as to adjust the solution at a concentration of 10 mM Ca^{++} . The present compound to be tested was applied to the specimen which had been maximally contracted and was evaluated for its relaxing activity. The results obtained are shown in Table 5.

Table 5

Calcium antagonistic activity

Compound No.	Minimum effective concentration (μ M)
1	1
13	3
14	1
15	0.3
19	0.3
20	0.3
26	1
30	0.3
31	1
47	0.1
50	0.3
63	0.3
64	0.3
89	0.3
93	0.03
102	0.03
103	0.1
114	0.1
116	0.03
121	0.03
diltiazem (Control)	0.3

Application example 2

Increasing activity of coronary blood flow

Male and female mongrel dogs weighing 8 to 17.5 kg were anesthetized with intravenous administration of sodium pentobarbital at a dosage of 30 mg/kg. Under artificial respiration the chest was opened on the left side at the level of the fourth intercostal space and the heart was exposed. The circumflex branch of left coronary artery just below the junction of the anterior descending branch of left coronary artery was isolated in a width of approximately 1 cm, and a flow probe was placed around this artery in order to measure the blood flow of the circumflex branch of left coronary artery by means of an electromagnetic flow meter. During the tests, systemic blood pressure was monitored, and data obtained from tests where the mean blood pressure was less than 65 mmHg were excluded from the final data. The pharmaceutical compound to be tested was dissolved in physiological saline or 50 % ethanol/50 % physiological saline and the thus obtained solution was intravenously administered at a dosage of 1 ml/10 kg through a polyethylene catheter which had been provided within the left femoral vein. The increasing activity of the blood flow of the circumflex branch of left coronary artery was evaluated and expressed in terms of increase rate of the blood flow after the administration of the compound to that of before the administration of the compound. The results obtained are shown in Table 6.

Table 6

Increase in coronary blood flow
(dog, 0.1 mg/kg iv)

Compound No.	Increase rate of coronary blood flow (%)
13	32.7
14	42.7
15	45.3
31	42.5
47	95.4
63	77.3
64	47.6
102	53.6
diltiazem (Control)	91.2

Application example 3

Antihypertensive activity

The compounds to be tested were administered orally to
evaluate antihypertensive activity in spontaneously
5 hypertensive rats (hereinafter SHR).

The average blood pressure of male SHR, 20 to 30 weeks
old, was measured in a non-anesthetised and non restraint
state, through a catheter which had been chronically
implanted into the abdominal aorta through the right
10 femoral artery, using an electromanometer. At the same
time, the heart rate was measured by a tachometer
triggered by the pulse pressure. The compound to be
tested was suspended in a 1 % tragacanth solution. After

the concentration of the suspensions was adjusted in a volume of 5 ml/kg, the compound was administered orally to the SHR. The blood pressure and heart rate were measured 0.5, 1, 3, 6 and 24 hours after the administration. The results are shown in Table 7.

Table 7

Antihypertensive activity

Comp. No.	Oral dosage (mg/kg)	Average blood pressure before administration	Increase rate of average blood pressure after administration (%)	
			after 1 hour	after 3 hours
47	10	188	-12	-3
50	10	190	-17	-7
82	10	190	-24	-15
102	10	187	-11	-2
diltiazem	30	185	-8	0
(Control)	100	186	-28	-14

Application example 4

Acute toxicity test

Tests were made using groups each comprising five male ICR strain mice weighing 30 to 35 g and being kept under a fast for 18 hours. The compound to be tested was suspended in a 1 % tragacanth solution. After the concentration of the suspensions was adjusted in a volume of 40 ml/kg, the compound was administered orally to the mouse. The results are shown in Table 8.

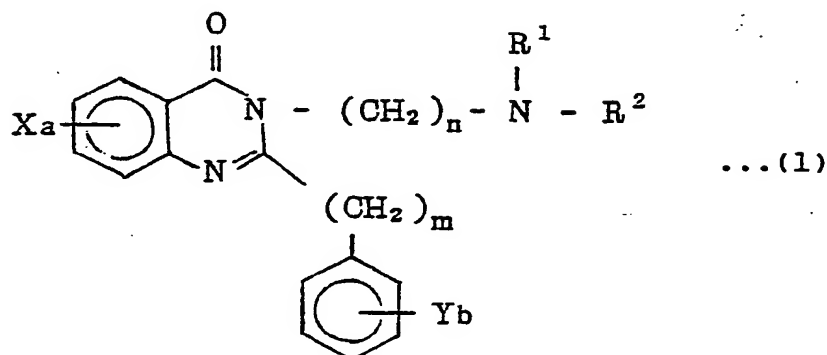
Table 8

Acute toxicity test (mouse, oral administration)

Comp. No.	LD50 (mg/kg)
13	700
31	1,000
47	750
50	700
63	1,200
82	750
102	1,000
diltiazem (Control)	650

Claims:

1. 2-Phenylalkyl-3-aminoalkyl-4(3H)-quinazolinone compound of Formula (1):



wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R¹ represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R² represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2) $-(CH_2)_\ell - \text{C}_6\text{H}_4 - Z^c$ [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R¹ and R² represent, together with the nitrogen atom to which they are attached, a cyclic amino group of the formula: $-\text{N} \begin{array}{c} \text{---} \end{array} \text{A}$ [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$]; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound of Formula (1) according to Claim 1, in which

5 X represents

10 a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an sec-butoxy group, an n-pentoxy group, a phenoxy group, a benzyloxy group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or a hydroxy group;

15 Y represents


20 a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group, a benzyloxy group, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom or a nitro group;

R¹ represents

25 a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, or a pentyl group;

R² represents

a methyl group, an ethyl group, an n-propyl, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, or a group of

5 Formula (2) $-(CH_2)_l$  (wherein, Z represents a hydrogen atom, a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, a sec-butyl group, a pentyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, a sec-butoxy group, an n-pentoxy group, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom); or

10

15 R¹ and R² represent, together with the nitrogen atom to which they are attached

an azilidino group, a pyrrolidino group, a piperidino group, a hexamethyleneimino group or a morpholino group,

20 3. The compound of Formula (1) according to Claim 2 in which

X represents

25 a hydrogen atom, a methyl group, an ethyl group, a chlorine atom, an iodine atom, a hydroxy group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-butoxy, an n-pentoxy group, an isopentoxy group, a phenoxy group, a chlorophenyl group or a methoxyphenoxy group when a is 1, or a dimethoxy group, a methoxy group and

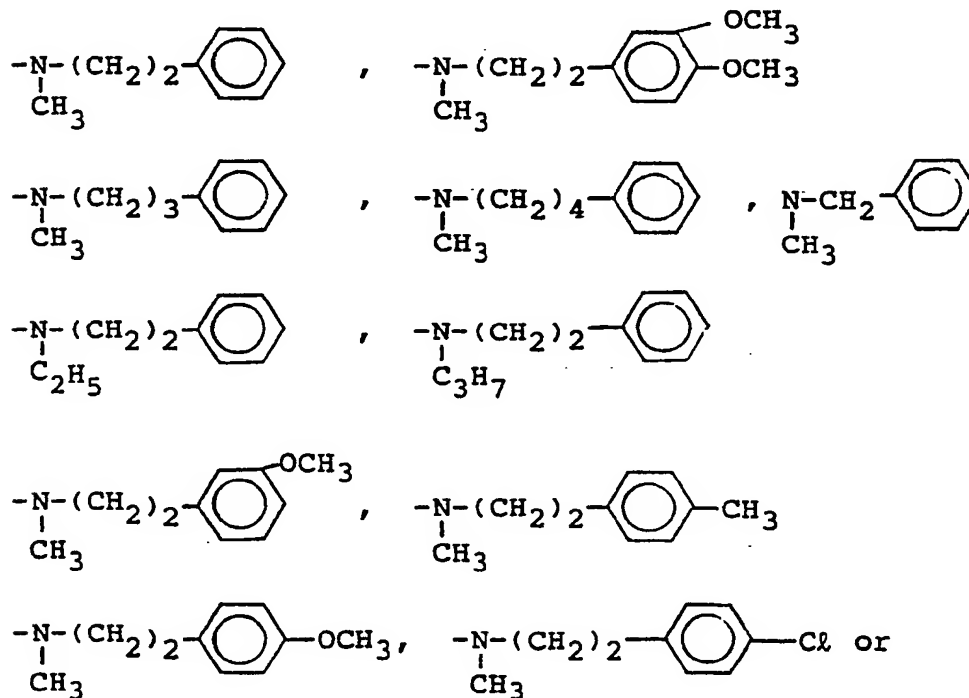
an ethoxy group or a methoxy group and an isopropyl group when a is 2.

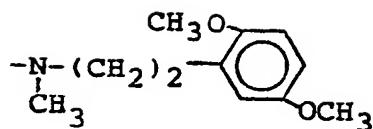
Y represents

- 5 a chlorine atom, a bromine atom, a methoxy group, an ethoxy group, a methyl group, a nitro group, a benzyloxy group, or an isopropoxy group when b is 1, or a dimethoxy group when b is 2.

$\begin{array}{c} \text{R}^1 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^2 \end{array}$ represents

- 10 a dimethylamino group, a pyrrolidino group, a diethylamino group, a morpholino group, a methylamino group, a cyclopentylamino group, a hexamethyleneimino group,

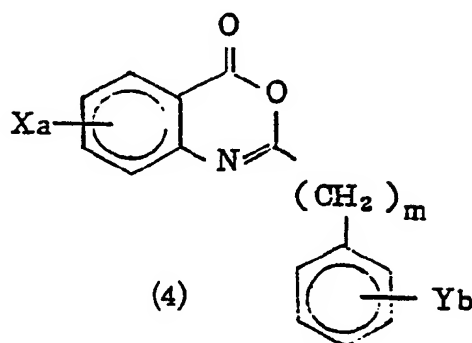




4. The compound of Formula (1) according to Claim 3, wherein the compound of Formula (1) is one selected from the group consisting of
- 2-(2,5-Dimethoxyphenylmethyl)-3-(3-dimethylaminopropyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.30),
 - 2-(2,5-Dimethoxyphenylmethyl)-3-(2-pyrrolidinylethyl)-6-methyl-4(3H)-quinazolinone (Compound No.31),
 - 2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.47),
 - 2-(4-Methoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-4(3H)-quinazolinone (Compound No.50),
 - 2-(2,5-Dimethoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-7-methoxy-4(3H)-quinazolinone (Compound No.81),
 - 2-(4-Methoxyphenylmethyl)-3-(2-dimethylaminoethyl)-6-isopropoxy-7-methoxy-4(3H)-quinazolinone (Compound No.82),
 - 2-(2,5-Dimethoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-4(3H)-quinazolinone (Compound No.93),
 - 2-(4-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-4(3H)-quinazolinone (Compound No.112),
 - 2-(4-Methoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-6-isopropoxy-4(3H)-quinazolinone (Compound No.118) and
 - 2-(2,5-Dimethoxyphenylmethyl)-3-[2-{N-(3,4-dimethoxyphenylethyl)-N-methylamino}-ethyl]-6-isopropoxy-4(3H)-quinazolinone (Compound No.120).

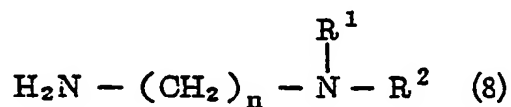
5. A process for preparing the compound of Formula (1) in Claim 1 which comprises

reacting a compound of Formula (4)



5 wherein X, Y, a, b and m have the same meanings as defined in Claim 1,

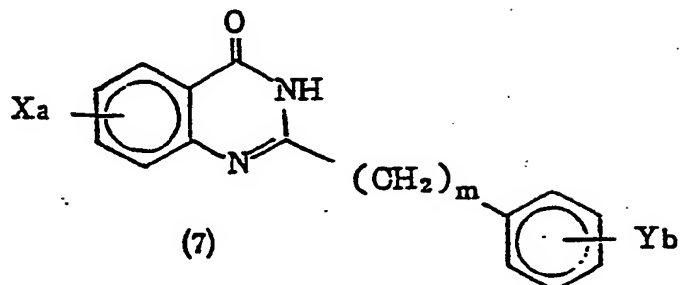
with a diamine of Formula (8)



wherein R^1 , R^2 and n have the same meanings as defined in Claim 1.

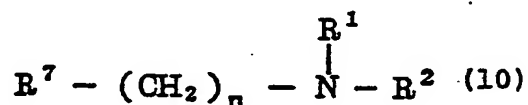
10 6. A process for preparing the compound of Formula (1) in Claim 1 which comprises

reacting a compound of Formula (7)



wherein X, Y, a, b and m have the same meanings as defined in Claim 1,

with an amine represented by Formula (10)



5 wherein R^1 , R^2 and n have the same meanings as defined in Claim 1, and R^7 represents a halogen atom or a mesyloxy group or a tosyloxy group.

7. A pharmaceutical composition which
comprises the compound of Formula (1) in Claim 1 or a
10 pharmaceutically acceptable acid addition salt thereof as
an active ingredient, and a pharmaceutically acceptable
carrier.

8. The composition according to Claim 7, wherein the
compound of Formula (1) in Claim 1 is one in Claim 2.

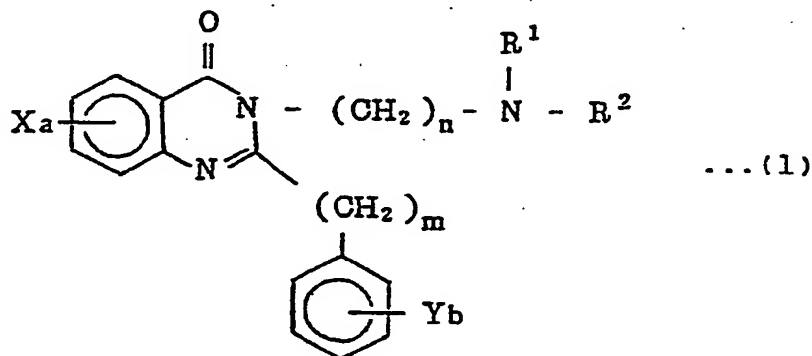
15 9. The composition according to Claim 8, wherein the
compound of Formula (1) in Claim 2 is one in Claim 3.

10. The composition according to Claim 9, wherein the compound of Formula (1) in Claim 3 is one in Claim 4.

11. The use of the compound of Formula (1) in Claim 1
or its pharmaceutically acceptable acid addition salt
5 for the preparing of a pharmaceutical composition for
dilating blood vessels or reducing the level of blood
pressure based on calcium antagonistic activity.

Claims for Austria

1. A process for preparing 2-Phenylalkyl-3-amino-alkyl-4(3H)-quinazolinone compounds for Formula (1):



15 wherein, X represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a phenoxy group, a benzyloxy group, a halogen atom or a hydroxy group; Y represents an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a benzyloxy group, a halogen atom or a nitro group; R¹ represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; R² represents an alkyl group having 1 to 5 carbon atoms or a group of Formula (2) $-(CH_2)_\ell - \text{C}_6\text{H}_4 - Z^c$ [wherein, Z represents a hydrogen atom, an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom; c is an integer of 1 to 3; and ℓ is an integer of 1 to 5]; or R¹ and R² represent, together with the nitrogen atom to which they are attached, a cyclic amino group of the formula: $-\text{N} \begin{array}{c} \text{---} \end{array} \text{A}$ [wherein, A represents an alkylene group having 2 to 6 carbon atoms or a group of the formula $-(CH_2)_2-O-(CH_2)_2-$; a and b are independently an integer of 1 to 3; and n and m are independently an integer of 1 to 5,

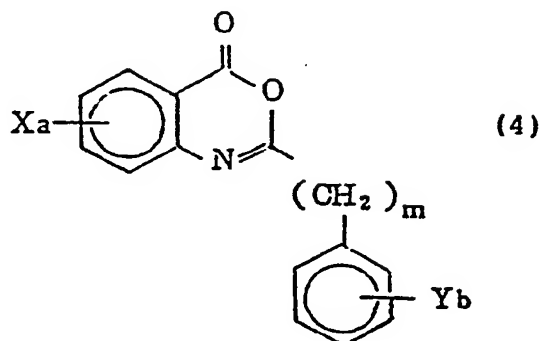
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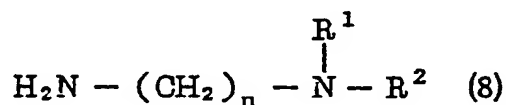
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characterized by reacting a compound of Formula (4)



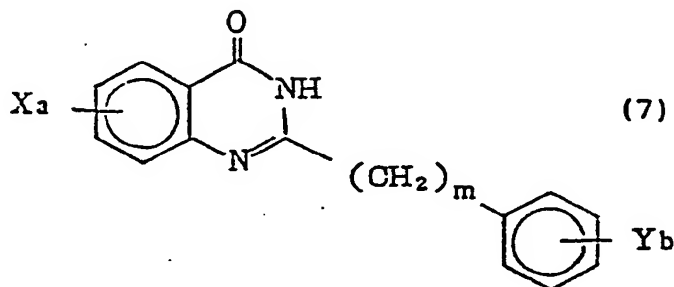
wherein X, Y, a, b and m have the meanings as defined hereinabove,

15 with a diamine of Formula (8)



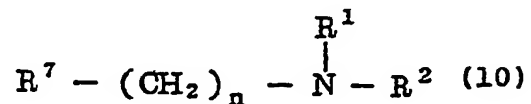
wherein R¹, R² and n have the meanings as defined hereinabove.

25 2. A process for preparing the compound of Formula (1) in Claim 1 which comprises reacting a compound of Formula (7)



wherein X, Y, a, b and m have the same meanings
as defined in Claim 1,

with an amine represented by Formula (10)



10

wherein R^1 , R^2 and n have the same meanings as
defined in Claim 1, and R^7 represents a halogen
atom or a mesyloxy group or a tosyloxy group.

15

3. The use of the compound of Formula (1) in Claim 1
or its pharmaceutically acceptable acid addition salt
for the preparing of a pharmaceutical composition for
dilating blood vessels or reducing the level of blood
20 pressure based on calcium antagonistic activity.